EXHIBIT A

American Journal of Therapeutics 5, 413–419 (1998)

Mechanisms Offsetting the Beneficial Effects of Antihypertensive Drugs: A Problem Increasingly Considered but Incompletely Understood

T.J.M. Cleophas

In clinical practice it is far from uncommon that antihypertensive drugs fail to meet their expectations. This is mainly due to mechanisms counteracting their antihypertensive effects. These mechanisms include stimulation of the sympathetic nervous system (SNS), inhibition of the parasympathetic nervous system (PSNS), stimulation of the renin-angiotensin-aldosterone system (RAAS), as well as endothelium-dependent mechanisms. To review whether the activation of such mechanisms follows differential patterns depending on the type of antihypertensive therapy being used. The antihypertensive effects of diuretics and calcium channel blockers are largely offset by all of the mechanisms enumerated. The antihypertensive effects of angiotensin-converting enzyme (ACE) inhibitors/angiotensin II (AII) receptor antagonists and β-blockers are counteracted by all of the mechanisms enumerated except for the effects of a stimulated RAAS and SNS, respectively. ACE inhibitors/AII receptor antagonists and β-blockers display a better profile of mechanisms counteracting their antihypertensive effects than other categories of drugs currently available. However, because this is not routinely confirmed by random trial evidence, additional determinants of drug performance must be considered including between-subject disparities in drug response, metabolic effects, and proliferative effects.

Keywords: hypertension, antihypertensive drugs, calcium channel blockers, diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists.

INTRODUCTION

In clinical practice, it is not uncommon for antihypertensive drugs to fail to meet their expectations. This failure is mainly due to mechanisms counteracting their antihypertensive effects. Arterial blood pressure is the product of cardiac output (CO) and total peripheral resistance (TPR) to blood flow through the vascular system. Heart rate and myocardial contractility are important determinants of CO. Vascular resistance is directly related to the viscosity of blood and length of blood vessels. Vascular resistance is inversely related to blood vessel luminal diameter, which normally represents the principal determinant of flow resistance. Cardiac performance and vascular diameter are controlled by several intrinsic regulatory mechanisms. Heart rate is determined by pacemaker cells in the sinoatrial node, and cardiac stroke volume is subject to several types of homeostatic regulation. The diameter of most resistance-producing blood vessels is influenced by the normal contractile state of the vessels balanced by release of vasorelaxant substances from the endothelial cell monolayer lining the vessel lumen. Patients with recent-onset essential hypertension tend to have an elevated CO. With chronic sustained hypertension, most patients develop normal or low CO and a fixed elevated peripheral resistance. Drugs currently available lower blood pressure by decreasing either CO or TPR. CO and TPR are not independent variables, however, and changes in one directly affect the other. Reduction of blood pressure activates physiologic mechanisms opposing a drug-induced decrease in blood pressure. Novel molecular techniques, for example, the identification of mRNAs of different blood

Department of Medicine, Merwede Hospital, Dordrecht, Netherlands.
Address for correspondence: Department of Medicine, Merwede Hospital, P.O. Box 306, Dordrecht, Netherlands 3300AH.

Table 1. Possible mechanisms opposing drug-induced decreases of blood pressure.

Endothelium independent	Endothelium dependent
Increased sympathetic activity (via baroreflex)	Decreased shear stress causing decreased endothelial release of*
Positive ino- and chronotropic	NO
Vasoconstriction	Vasodilatory prostaglandins
Inhibition of parasympathetic activity	Natriuretic peptides
(via baroreflex)	Endothelium-derived hyperpolarization factor
Positive chronotropic	Decreased vasodilation
Decreased vasodilation	Increased Na, K, H_2O excretion
(acetylcholine mediated)	Decreased shear stress causing increased secretion of*
Increased renin-angiotensin-aldosterone	Vasoconstrictive eicosanoids (thromboxanes)
secretion	Substance P†
Na, K, H_2 retention	Endothelins
Vasoconstriction	Vasoconstriction
Increased ADH/vasopressin secretion	Reduced activity of other endothelium-dependent vasoactive
(via baroreflex)	compounds that influence NO-mediated vasodilation*
Na, K, H_2O retention	Acetylcholine (PSNS nerve endings)
Vasoconstriction	Adenosine triphosphate
Direct intrarenal hydraulic effect	Bradykinin (mast cells)
Na, K, H_2O retention	Histamine (mast cells)
Other endothelium-independent	Decreased vasodilation
circulating vasoactive compounds*	
Dopamine (SNS)†	
Adrenaline (adrenal gland)†	
Ca^{++}	
K	
Serotonin (platelets)†	

Abbreviations: NO, nitric oxide; SNS, sympathetic nervous system; PSNS, parasympathetic nervous system.
*More recently considered mechanisms. Some of the compounds mentioned here are not discussed in the text, and the extent of their influence on the effects of hypotensive drugs is based on indirect arguments and is partly theoretical.
†Compound produces, in addition to vasoconstrictor, vasodilator activity.

pressure–modulating factors through polymerase chain reaction, have greatly expanded insight into these mechanisms. This article reviews such mechanisms. It is concluded that they follow differential patterns depending on the type of antihypertensive therapy being used and that β-blockers and angiotensin-converting enzyme (ACE) inhibitors display a better profile in this respect than other categories of drugs currently available.

PHYSIOLOGIC MECHANISMS OPPOSING DRUG-INDUCED DECREASES OF BLOOD PRESSURE

See Table 1 for mechanisms that oppose drug-induced decreases of blood pressure.

Renin-angiotensin-aldosterone system

A decrease in arterial pressure causes release of the enzyme renin from the kidney into the blood. Renin generates angiotensin I from a circulating substrate, angiotensinogen, synthesized in the liver and other tissues. Angiotensin I is converted to angiotensin II (AII) by *converting enzyme*, found in the endothelial cells of the lung as well as other tissues. AII constricts blood vessels and causes renal salt and water retention by direct intrarenal actions and by stimulating the adrenal gland to release the potent mineralocorticoid aldosterone.

Sympathetic nervous system

A decrease in blood pressure also activates the baroreflex, producing increases in sympathetic nervous system activity and leading to (1) increased forced and rate of cardiac contraction and enhanced cardiac relaxation, which combine to elevate CO; (2) constriction of resistance arteries leading to an increase in TPR; and (3) renal retention of sodium chloride and water, a mechanism mediated by renal sympathetic nerves innervating renal blood vessels and tubules.

Parasympathetic nervous system

Inhibition of parasympathetically mediated heart rate changes occurs within 1 second when blood pressure

acutely drops, whereas sympathetically mediated changes do not occur until after 1 to 2 minutes.[1] It is an important defense against orthostatic hypotension as well as acute hypotension after intravenous or sublingual administration of hypotensive agents. Vagal inhibition through the baroreflex may be an initial step to the deleterious effects of acute tachycardias after the acute administration of vasodilators such as nifedipine.

Vasopressin system

A decrease in arterial pressure causes baroreflex-mediated release of vasopressin (antidiuretic hormone [ADH]), which is a trigger to vasoconstriction and acts on the renal collecting ducts to enhance retention of water.

Fluid retention by the kidney

A fall in arterial pressure causes decreased sodium chloride and water excretion by the kidney. This decrease results, in part, from the direct intrarenal hydraulic effect of reduced renal perfusion pressure and, in part, from the other mechanisms just listed. The resultant expansion of extracellular fluid and plasma volume tends to increase CO and arterial pressure and thus reduce the antihypertensive action of the drug.

RECENTLY RECOGNIZED MECHANISMS OPPOSING DRUG-INDUCED DECREASES OF BLOOD PRESSURE

Endothelium-independent factors

Important vasoconstrictor activity is displayed by serotonin.[2] It is released from the sympathetic nuclei in the central nervous system and from platelets in the vessels. Serotonin, similar to norepinephrine and AII, causes vasoconstriction mediated by the second messengers inositol triphosphate and diacylglycerol, enhancing Ca^{++} influx through the ion-voltage Ca^{++} channels as well as Ca^{++} influx from subcellular compartments, such as the sarcoplasmic reticulum.[3] Another endothelium-independent vasoactive mechanism is the cyclic adenosine monophosphate–mediated stimulation of Ca^{++} efflux caused by the α_2-agonist and β_2-agonist epinephrine,[4] dopamine,[5] and some prostaglandins[6] through action at their different receptors on the vascular smooth muscle cells. Particularly, nonselective β-blockers are considered to produce paradoxic pressor effects because of inhibition of the latter mechanism.[7] A recently recognized but poorly understood mechanism counteracting drug-induced decreases in blood pressure is the so-called sustained myogenic tone in resistance arteries, which is endothelium independent and calcium mediated.[8,9]

Endothelium-dependent factors

Autocrine and paracrine factors involved in the regulation of endothelium-dependent and endothelium-independent myocardial and vascular muscle cell tonus have been recognized, but their mechanism has not yet been clearly defined. Although the sympathetic nervous system (SNS) acts independently of the vascular endothelium,[10] the renin-angiotensin-aldosterone system (RAAS),[11] and the parasympathetic nervous system (PSNS)[12] do not (Table 1): AII stimulates vascular smooth muscle cells directly through its receptors and, in addition, modulates the release of both nitric oxide (NO)[13] and endothelins[14] from endothelial cells. Acetylcholine released from the PSNS nerve endings produces mainly a receptor-mediated stimulation of NO synthetase[15] in the intact endothelium. A reduction in shear stress by antihypertensive drugs triggers the endothelium to start releasing several vasoconstrictors, including thromboxanes and endothelins, and to stop releasing vasorelaxants, including NO, prostaglandins, C type natriuretic peptide, and endothelium-derived hyperpolarization factor[16,17] (Table 1), the latter of which is particularly important when NO release is impaired.[18] Many patients with hypertension have impaired vasodilation of resistance arteries because of endothelial dysfunction.[19] Although this phenomenon does not oppose drug-induced decreases of blood pressure, it may contribute to small responses to drug treatment in some of these patients.

FREQUENTLY USED ANTIHYPERTENSIVE DRUGS AND SPECIFIC MECHANISMS OFFSETTING THEIR ANTIHYPERTENSIVE ACTIVITIES

Diuretics

Although the antihypertensive activity of diuretics is not completely understood, they obviously cause salt and subsequently blood volume depletion. Salt restriction brings about a 10% reduction in arterial blood pressure as demonstrated in the Intersalt Study, an effect that is lost in patients who increase their dietary salt.[20] In patients who do not increase their salt intake,

Table 2. Schematic pattern of how different mechanisms possibly oppose the effects of frequently used antihypertensive drugs.

	Diuretics	ACE inhibitors	Calcium channel blockers	β-Blockers
RAAS stimulation	↑	↓	↑	↓
SNS stimulation	↑	↑	↑	↓
PSNS inhibition	↑	↑	↑	↑
Endothelium-dependent mechanisms*	↑	↑	↑	↑

Abbreviations: RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; PSNS, parasympathetic nervous system.
*The influence of specific mechanisms and the extent of their influence are based on indirect arguments and are partly theoretical.

the antihypertensive effect is largely offset by almost all of the mechanisms enumerated in Table 1, of which the increased activities of the RAAS and SNS[21] probably are most important because these activities have been strongly associated with the deleterious effects of long-term hypertension, such as occlusive arterial disease, cardiac failure, and cardiac death. This is consistent with the study of Alderman et al[22] in 3000 hypertensive subjects establishing a fivefold increased susceptibility to myocardial infarction in salt-depleted subjects. Table 2 shows not only that β-blockers and ACE inhibitors activate fewer counterbalance mechanisms than the other categories do, but also that they either do not activate the RAAS and SNS or do so to a lesser degree.

ACE inhibitors and AII receptor antagonists

The exact mechanisms of action of ACE inhibitors and AII receptor antagonists are not well known. They not only inhibit the production or activity of AII, but also potentiate prostaglandin-mediated and bradykinin-mediated vasodilator activity.[23] This synergism results in a reduction of the peripheral vascular resistance by dilation of the resistance vessels. Although all of the mechanisms from Table 1 except the effects of the RAAS may be important in counteracting this synergism, some of them have been postulated to be particularly so. First, in contrast to the SNS, which exerts its action directly on the cardiovascular smooth muscle cells, the RAAS interacts with the AT_1 receptors that are present on both the cardiovascular endothelium and smooth muscle cells.[24] Stimulation of the endothelial AT_1 receptors modulates the release of both endothelins and NO.[25] Reduced activation of these receptors by ACE inhibitors is associated with increased levels of NO and reduced levels of endothelins. This mechanism would explain the decreased sensitivity of the resistance vessels to AII commonly seen with ACE inhibitors.[26] Second, ACE inhibitors caused an increase of sympathetic activity through baroreflex activation, although this effect was lacking in the kidney[11] and was less substantial than seen with calcium channel blockers.[27] One of the reasons for the difference in baroreflex activation may be the absence of modulatory calcium channel receptors and presence of AT_1 receptors on the vascular endothelium.[28] In contrast to ACE inhibitors, AT_1 receptor blockers have been demonstrated to increase not only plasma norepinephrine levels,[29] but also renal sympathetic activity.[30]

Calcium channel blockers

Increase of CA^{++} influx into the muscle cell causes vasoconstriction. Calcium channel blockers block Ca^{++} entry into the vascular smooth muscle cell through the L-type ion-gated Ca^{++} channels. The intracellular Ca^{++} concentration is a final common pathway of contraction, although NO can decrease the sensitivity of contractive proteins to Ca^{++}, and so calcium channel blockers exert an important influence on this mechanism.[31] The vasodilation that follows their administration raises a baroreflex-mediated counterbalance, mediated by a change in the balance between the PSNS and the SNS and increased ADH secretion.[32] The resulting tachycardia[33] and volume expansion[34] are further amplified by fluid retention because of intrarenal hydraulic properties[35] as well as activation of the RAAS.[36] It has been assumed that such mechanisms would not be so active if sustained-release formulations instead of short-acting calcium channel blockers were applied.[37] Sustained-release nicardipine, however, caused an increased plasma concentration of AII and increase of SNS activity similar to acute-release nifedipine.[27] These counterbalance mechanisms overcame vasodilation in a number of studies.[38]

β-Blockers

β-Blockers have a favorable profile of counterbalance mechanisms. They reduce sympathetically mediated stimulation of CO and reduce RAAS by reducing renin activity in the kidney.[39] In this regard, their efficacy is similar to that of ACE inhibitors, but in addition they do not allow for an increased sympathetic activity in the heart because the cardiac β-receptors are blocked. Also, β-blockers have been demonstrated to stimulate vasodilatory prostaglandins.[40] Particularly the cardioselective β_1 property is considered responsible for the hemodynamic benefit because, in contrast to the β_2 property, it allows for β_2-receptor mediated vasodilation.[41]

DISCUSSION

Increased SNS and RAAS as well as serotonin activity increases the mRNA expression of *c-fos*, *c-jun*, and *c-myc* proto-oncogenes, and these systems are thus mitogens. They induce growth factors, such as insulin, vascular endothelial growth factor, and cytokines.[42–44] These factors have been associated with left ventricular hypertrophy, remodeling, atherosclerosis, and apoptosis, all of which are mechanisms considered important causes of morbidity and mortality from long-term hypertension. The importance of these factors is emphasized by the insulin-resistant syndrome X, which combines early hypertensive tissue damage with initially virtual absence of elevated blood pressure.[45] Drugs that suppress one or more of the mechanisms promoting mitogenesis may be advantageous in the long-term compared with others. β-Blockers provide the best profile in this respect because they block the adrenergic receptors in the heart as well as the renin receptors in the kidney. The stimulation of β-receptors could be a primary effector of the mitogen mechanism in the heart.[46] Cardioselective β-blockers do not antagonize stimulation of β_2-receptors on the vascular smooth muscle cells, enhancing cyclic adenosine monophosphate–mediated Ca^{++} efflux, which promotes relaxation[47]: ACE inhibitors and AII receptor blockers, although they inhibit action of the RAAS, do not prevent action of the SNS and PSNS. A poor profile is displayed by the calcium channel blockers and diuretics, which give rise to increase of all of the three mitogen mechanisms. There is some evidence in the literature that such considerations are of clinical importance.[38] Furberg et al[48] showed in their case-control study an increased risk of myocardial infarction in patients with hypertension treated with calcium channel blockers by 60% ($P < 0.001$), an unchanged risk in those treated with ACE inhibitors, and a decreased risk by 30% ($P < 0.04$) in patients treated with β-blockers. The β-blocker data were consistent with the existent data from the large primary and secondary β-blocker prevention studies, and the calcium channel blocker data were subsequently confirmed by a meta-analysis of calcium blocker trials from the same authors.[49]

The beneficial effect of diuretics on blood pressure has never been strongly associated with a beneficial effect on survival and has even been connected with increased risk of death in recent research.[20] The effect of diuretics is small in practice because of patients' reluctance to limit their salt intake.[50] In compliant patients, diuretics caused an increase of all of the growth factor–enhancing mechanisms.[51] The acute effect of calcium channel blockers is counteracted by vagal inhibition in addition to increased sympathetic activity, giving rise to particularly dangerous tachycardias,[35,37] which is generally considered to be responsible for cardiovascular complications such as myocardial infarction.[52] Although calcium channel blockers are approved as safe antihypertensive drugs, caution must be exercised because of their reflex parasympathoinhibition and sympathoactivation to blood pressure reduction.[53] In this regard, AII receptor antagonists and the newer class of calcium channel blockers have been thought to be promising for long-term treatment because those drugs provide good bioavailability with once-daily dosing and might induce less reflex sympathoactivation, but evidence from controlled clinical trials is largely missing. Diuretics as well as calcium channel blockers are associated with less favorable counterbalance mechanisms than β-blockers or ACE inhibitors, the first of which displays the best performance in this respect.

Drugs that exert a central inhibitory effect on the SNS, such as the α_2-agonists clonidine[54] and moxonidine,[55] or the recently developed serotonin inhibitors, such as ketanserin,[56] either as a single treatment or in combination with low dosages of other inhibitors or blockers of the RAAS and SNS may be efficient alternatives to the current regimens with fewer side effects. Current NO donors are antiproliferative[57] but did not lower blood pressure to acceptable levels in patients with hypertension.[58] Different treatment regimens with asymmetric dosages of NO donors are documentedly efficient in angina pectoris and may also be so in hypertension with its circadian rhythm similar to that of angina pectoris.[59] The counterbalance profiles of NO donors have not been extensively studied. Because of the antiproliferative properties of NO in ani-

mal testing, however, they deserve attention. This is even more so because rather than the level of blood pressure, the activation of counterbalance mechanisms and the absence of such activation are probably important determinants of long-term benefit or lack of benefit from antihypertensive drug treatment. The purpose of treatment of hypertension is to prevent cardiovascular complications, including atherosclerosis and ischemic heart disease. Drug treatment has been shown through controlled clinical trials to reduce the morbidity and mortality associated with hypertension. Yet the benefit of drug treatment is less than predicted from epidemiologic surveys. The question as to whether any specific drug class confers harm in addition to benefit for the treatment of hypertension is the objective of several current trials. The Treatment of Mild Hypertension Study (THOMHS) trial,[59] although designed to address this question, was not sensitive to provide reliable estimates of its end points. The ongoing Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[60] from the same investigators included not less than 40,000 patients to provide enough sensitivity. In my view, no trial whatever size will ever find the definite answer, unless the specific counterbalance mechanisms of the drugs under study are assessed more systematically.

REFERENCES

1. Wieling W: Reflex control heart rate in normal subjects in relation to age: a data base for cardiac vagal neuropathy. Diabetologia 1982;22:163–166.
2. Hollenberg NK: Serotonin and vascular responses. Annu Rev Pharmacol Toxicol 1988;28:41–59.
3. Nishimura J, van Breemen C: Direct regulation of smooth muscle contractile elements by second messengers. Biochem Biophys Res Commun 1989;163:929–939.
4. Houben H, Thien T, van't Laar A: Effects of low-dose epinephrine infusion on hemodynamics after selective and non-selective beta-blockade in hypertension. Clin Pharmacol Ther 1982;31:685–690.
5. Goldberg LI, Rajfer EI: Dopamine receptors, applications in clinical cardiology. Circulation 1985;72:245–248.
6. Fitzgerald GA, Murray R, Moran N: Mechanisms of eicosanoid action. Adv Prostaglandin Thromboxane Leukot Res 1991;21B:577–580.
7. Cleophas TJM, Kalmansohn RB: To beta-block or better block. Br Med J 1996;11:167–168.
8. Garcia SR, Bund SJ, Izzard AS, et al: Myogenic tone in resistance arteries from spontaneously hypertensive rats. J Vasc Res 1996;33(Suppl 2):42.
9. Koller A, Huang A, Sun D: Endothelium independent factors augment myogenic tone in hypertension. J Vasc Res 1996;33(Suppl 2):7.
10. Saruta T, Kumagai H: The sympathetic nervous system in hypertension and renal disease. Curr Opin Nephrol Hypertens 1996;5:72–80.
11. Braam B, Koomans HA: Renal responses to antagonism of the renin-angiotensin system. Curr Opin Nephrol Hypertens 1996;5:89–97.
12. Cleophas TJM: A pressor effect of non-selective beta-blockers in diabetics with postural hypotension. In: Beta-Blockers in Hypertension and Angina Pectoris (Ed Cleophas TJM), Kluwer Academic Publishers, Dordrecht, Netherlands, 1995, pp 34–44.
13. Baylis C, Vallance P: Nitric oxide and blood pressure: Effects of nitric oxide deficiency. Curr Opin Nephrol Hypertens 1996;5:80–89.
14. Hiruda Y: Endothelin peptides. Curr Opin Nephrol Hypertens 1996;5:12–16.
15. Taddei S, Virdis A, Mattei P, et al: Vasodilation to acetylcholine in primary and secondary forms of human hypertension. Hypertension 1993;21:929–933.
16. Hayashi K, Loutzenhiser R, Epstein M, et al: Multiple factos contribute to acetylcholine-induced renal afferent arteriolar vasodilation during myogenic and norepinephrine- and KCL-induced vasoconstriction. Circ Res 1994;75:821–828.
17. Kanai AJ, Strauss HC, Truskey GA, et al: Shear stress induces ATP-independent nitric oxide release from the vascular endothelial cells. Circ Res 1995;77:284–293.
18. Bauersachs J, Popp R, Hecker M, et al: Attenuated nitric oxide release triggers the release of endothelium derived hyperpolarizing factor. Circulation 1996;94:3341–3347.
19. Lerman A, Burnett JC Jr: Intact and altered endothelium in regulation of vasomotion. Circulation 1992;86(Suppl 3):12–19.
20. Intersalt Cooperative Research Group: Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium excretion. Br Med J 1988;247:319–328.
21. Cook NB, Cutter JA, Hennekens CH: An unexpected result for sodium causal or casual? Hypertension 1995; 25:1154–1155.
22. Alderman MH, Madhaven S, Cohen H, et al: Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. Hypertension 1995;25:1144–1152.
23. Mitchell KD, Braun B, Navar LG: Hypertensinogenic mechanisms mediated by the intrarenal actions of renin-angiotensin system. Hypertension 1992;19(Suppl 1):18–27.
24. Taddei S, Virdis A, Mattei P, et al. Angiotensin II and sympathetic activity in sodium-restricted essential hypertension. Hypertension 1995;25:595–601.
25. Townend JM, Al-Aui M, West JN, et al: Modulation of cardiac automatic control in humans by angiotensin II. Hypertension 1995;25:1270–1275.
26. Braun B, Koomans HA: Nitric oxide antagonizes the actions of angiotensin II to enhance tubuloglomerular feedback responsiveness. Kidney Int 1995;48:1406–1411.
27. Kumagai H, Suzuki H, Ischikawa M, et al: Different responses of blood flow and sympathetic nerve activity to

captopril and nicardipine in conscious renal hypertensive rabbits. J Cardiovasc Pharmacol 1995;25:57–64.
28. Takishita S, Muratani H, Sesoko S, et al: Short-effects of angiotensin II blockade on renal blood flow and sympathetic activity in awake rats. Hypertension 1994;24:445–450.
29. Kamagai K, Reid IA: Angiotensin II exerts differential actions on renal nerve activity and heart rate. Hypertension 1994;24:451–456.
30. Van den Meiracker AH, Admiraal PJ, Jansen JA, et al: Hemodynamic and biochemic effects of the AT_1 receptor antagonist irbesan in hypertension. Hypertension 1995; 25:22–29.
31. Bevan JA, Bevan RD, Huo J, et al: Calcium, intrinsic and extrinsic myogenic tone. In: *International Symposium on Calcium Modulators* (Eds Godfraind T, Albertini A, Paoletti R), Elsevier Biomedical Press, Amsterdam, 1982, pp 125–132.
32. Lehmann HV, Hochrein H, Witt E, et al: Hemodynamic effects of calcium antagonists. Hypertension 1983;5:66–73.
33. Frishman WH, Stroh JA, Greenberg SM, et al: Calcium channel blockers in systemic hypertension. Curr Probl Cardiol 1987;12:285–346.
34. Weir MR, Dzau VJ, Sasamura H, et al: Efficacy, tolerability, and quality of life of losartan versus nifedipine GITS in patients with essential hypertension. Clin Ther 1996;18:411–428.
35. Ruzicka M, Leenen FHH: Relevance of intermittent increases in sympathetic activity for adverse outcome on short-acting calcium antagonists. In: *Hypertension, Pathophysiology, Diagnosis and Management* (Eds Laragh JH, Brenner BM), Raven Press, New York, 1995, pp 2815–2825.
36. Francis GS: Calcium channel blockers and congestive heart failure. Circulation 1991;83:336–338.
37. Packer M: Pathophysiological mechanisms underlying the adverse effects of calcium-channel blocking drugs in patients with chronic heart failure. Circulation 1989;80:59–67.
38. Cohen JD: 1995: the year of the calcium antagonist controversy. Curr Opin Nephrol Hypertens 1996;5:214–218.
39. *The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.* NIH Publication no. 93-1088, 1993.
40. Smith WL: The eicosanoids and their biochemical mechanisms of action. Biochem J 1989;259:315–320.
41. Johnson DB, Dell Italia LJ: Cardiac hypertrophy and failure in hypertension. Curr Opin Nephrol Hypertens 1996;5:186–191.
42. Ferrara N, Bunting S: Vascular endothelial growth factor, a specfic regulator of angiogenesis. Curr Opin Nephrol Hypertens 1996;5:35–45.
43. Amann K, Ritz E: Cardiac structure and function in renal disease. Curr Opin Nephrol Hypertens 1996;5:102–106.
44. Wareham NJ, Byrne CD, Hales CN: Role of insulin and proinsulin in diabetic vascular disease. Metabolism 1995;44(Suppl 4):76–82.
45. Atkins FL, Bing OHL, DiMauro PG, et al: Modulation of ventricular beta-adrenergic receptors from spontaneously hypertensive rats with left ventricular hypertrophy and failure. Hypertension 1995;26:78–82
46. Westphall D, Gerthoffer WT: Vasodilators. In: *Human Pharmacology* (Eds Brady JM, Larner J, Minnemann KP, et al), 1994, Mosby-Year Book, St. Louis, pp 215–223.
47. Psaty BM, Heckbert SR, Koepsell TD, et al: The risk of myocardial infarction associated with anti-hypertensive drugs therapies. JAMA 1995;274:620–625.
48. Furberg CD, Psaty BM, Meyer JV: Nifedipine: dose-related increase in mortality in patients with coronary heart disease. Circulation 1995;92:1326–1331.
49. Hashimoto J, Imac Y, Minami N, et al: Compliance with long-term dietary salt-restriction in hypertensive outpatients. Clin Exp Hypertens 1994;16:729–739.
50. Wong FS, Miller JA, Blendis LM, et al: Effect of insulin on the vasoconstrictive responsc to norepinephrine in normal human subjects: the influence of sodium status. Am J Hypertens 1994;7:1097–1104.
51. Opie LH, Messerli FH: Nifedipine and mortality: grave defects in the dossier. Circulation 1995;92:1068–1073.
52. Lindqvist M, Kahan T, Melcher A, et al: Acute and chronic calcium antagonist treatment elevates sympathetic activity in primary hypertension. Hypertension 1994;24:287–296.
53. Frisk-Holmberg M, Paalzow L, Wibell L: Relationship between cardiovascular effects and steady-state kinetics of clonidine in hypertension. Eur J Clin Pharmacol 1984; 26:309–313.
54. van Zwieten TA, Hamilton CA, Prichard BNC: The I-1-Imidazoline Receptor Agonist Monoxidine, Roy Soc Med Services, Alden Press, Oxford, UK, 1994.
55. Vanhoutte P: Serotoninergic mechanisms in hypertension. focus on the effects of ketanserin. Hypertension 1988;11:111–133.
56. Garg VC, Hassid A: Nitric-oxide generating vasodilators and cyclic guanosin monophosphate inhibit mitogenesis of rat vascular smooth muscle cells. J Clin Invest 1989; 83:1774–1777.
57. Cleophas TJM, Niemeyer MG: No-donors and angina pectoris: more than just symptomatic treatment? Neth J Med 1998;52:82–89.
58. Cleophas TJM, Niemeyer MG, van de Wall EE, et al: Nitrate induced headache in patients with stable angina pectoris: beneficial effect of starting on a low dosage. Angiology 1996;47:812–823.
59. Grimm RH, Flack JM, Grandits GA, et al: Long-term effects of diet and drugs to treat hypertension. Treatment of Mild Hypertension Study (TOMHS) Research Group. JAMA 1996;275:1549–1556.
60. Elliott WJ: ALLHAT: the largest and most important clinical trial in hypertension ever done in the USA. Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial. Am J Hypcrtens 1996;9:409–411.